## REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 3, 4, 8-11, 16, 19, 22 and 23 are in the case.

## I. THE OBVIOUSNESS REJCTION

It is noted, with appreciation, that the obviousness rejection has been withdrawn.

## II. THE FORMAL REJECTION

Claim 16 stands rejected under 35 U.S.C. §112, first paragraph, on alleged lack of enablement grounds. In response, and without conceding to the rejection, claim 16 has been amended to state that the tumor cells have regions of hypoxia and express at least one endogenous nitroreductase enzyme to activate the compound of formula (IIIb) into an active metabolite to ablate the tumor cells. This wording provides greater focus on the need for at least regions of transient hypoxia to be present in the tumor in order for active metabolite(s) to be formed, and it is more consistent with the hypoxia-selective focus of the invention. Support will be clear the discussion below.

Referring to the lack of enablement rejection, attached are three published papers, all authored or co-authored by the inventors. The first is a publication from the British Journal of Cancer in 1996, entitled "Recent developments in the design of bioreductive drugs". This paper *inter alia* describes design considerations for various bioreductive drugs. One such consideration is the type of activation system. Beginning at the foot of the second column on page S32 and continuing in the first column on page S33, activation by endogenous enzymes (including by 1-electron reductases under

hypoxic conditions) is described. This section makes it clear that, in common with other tissues, tumor cells do contain (express) endogenous reductases, and that these enzymes are capable of activating prodrugs (including nitroaromatic prodrugs) to release a cytotoxic effector. Support for the fact that nitroreductases are endogenously expressed in tumors is therefore provided.

The second paper is from Nature Reviews, 2004, entitled "Exploiting tumour hypoxia in cancer treatment". This paper provides a general update on how hypoxia is targeted in cancer therapy. One strategy described is the development of prodrugs activated by hypoxia. An activation mechanism is shown in Figure 2 of the paper and involves intra-cellular 1-electron reduction of the prodrug to convert it to a radical under hypoxic conditions. In addition, Figure 4 describes the mechanism of hypoxic activation of prodrugs, with Figure 4c showing the 1-electron reduction of symmetrical nitrogen mustard SN 23862 to its corresponding cytotoxic amine. This mechanism of activation shown for the nitrogen mustard SN 23862 is equally applicable to the activation of the nitroaniline-based bromomesylate mustards of the present invention (conversion of the 2-nitro group to the corresponding amine by intra-cellular 1-electron reductases).

The third paper is from Clin. Cancer Res. (2007), entitled "Mechanism of Action and Preclinical Antitumor Activity of the Novel Hypoxia-Activated DNA Cross-Linking Agent PR-104". It describes the mechanism of action of the hypoxia-activated pre-prodrug PR-104. PR-104 is hydrolysed *in vivo* to release PR-104A which is a compound of formula (IIIb) as defined in claim 4. PR-104A itself is specifically claimed in claim 3. This paper describes the activation of PR-104A under hypoxia to release its cytotoxic metabolites and deliver an anti-tumour effect. This activation is without the

introduction of any exogenous reductase via a GDEPT or other approach. It is instead the result of activation by endogenous nitroreductases present/expressed within the tumour cells.

In summary, the attached papers disclose that:

(1) in common with other tissues, tumor cells express endogenous intra-cellular reductases;

(2) these intra-cellular reductases include those capable of reducing nitroraromatic complexes and therefore include nitroreductases;

(3) these nitroreductases are specifically capable of reducing nitroaniline-based mustard compounds generally (predominantly at the 2-nitro group) to form the corresponding reactive amine species;

(4) in the presence of oxygen, the reactive species is rapidly back-oxidised to the original nitroaniline-based prodrug;

(5) due to their uncontrolled growth, tumor cells generally exhibit at least transient hypoxia. Solid tumors in particular have significant regions of hypoxia;

(6) under hypoxia, back-oxidation of the reactive species to the original prodrug does not occur;

(7) the mustard prodrugs of the invention as claimed in claim 4 are thus selectively converted to cytotoxic species under the hypoxic conditions which prevail in tumors generally and in solid tumors in particular; and

(8) while this is evidenced for the prodrug PR-104A (the compound of formula (IIIb) specifically claimed in claim 3) in particular, the same mechanism applies to the activation of the other nitroaniline-based compounds of claim 4.

Based on the above, one of ordinary skill, as of the filing date of the present case, would have bee able to carry out the claimed invention without the exercise of undue experimentation. Withdrawal of the lack of enablement rejection is respectfully requested.

Favorable action is awaited.

Respectfully submitted,

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Attachments: British Journal of Cancer in 1996, entitled "Recent developments in the design of bioreductive drugs"; Nature Reviews (2004), entitled " Exploiting tumour hypoxia in cancer treatment"; Clin Cancer Res (2007), entitled "Mechanism of Action and Preclinical Antitumor Activity of the Novel Hypoxia-Activated DNA Cross-Linking Agent PR-104".